IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : B. Dentz
Art Unit : 121
Applicant : Roy Johnson, et al.
Serial No. : 200,690
Filed : 27 October 1980
For : PGI_2 PHARMACOLOGICALLY ACCEPTABLE SALTS

Commissioner of Patents and Trademarks
Washington, D.C. 20231

APPELLANTS' BRIEF UNDER 37 CFR 1.192(a)

Sir:

The following represents appellants' brief in triplicate as required under the provisions of 37 CFR 1.192(a). Authorization is hereby granted to charge the fee required under 35 USC 41(a)6 ($50.00) to deposit account 21-0718. An additional copy of this cover page is provided in connection with this authorization.

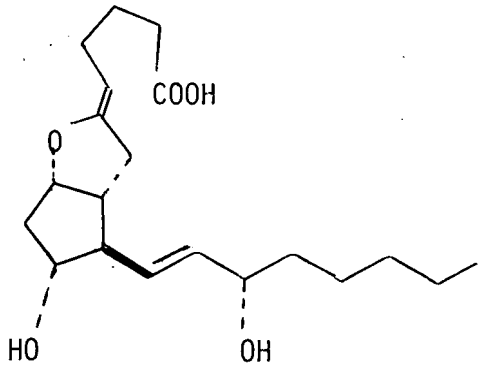
CLAIMS ON APPEAL

No claims are allowed in this application. The claims on appeal are the pending claims in this application, claims 1-6, a copy of which is attached hereto as an appendix.

CONCISE SUMMARY OF THE INVENTION

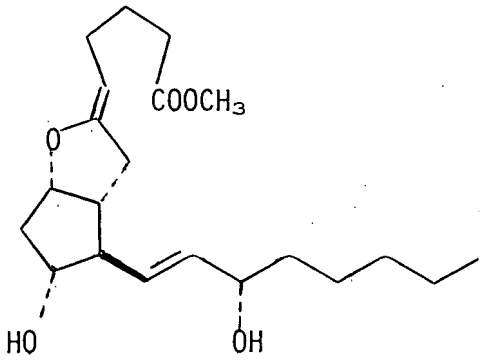
The present invention relates to substantially pure forms of the pharmacologically acceptable salts of prostacyclin and pharmaceutical compositions prepared therefrom. Prostacyclin itself is a naturally occuring hormonal substance. Prostacyclin was first isolated as an impure residue by Moncada and his co-workers in 1976. The chemical structure of prostacyclin was first elucidated by Johnson and his co-workers (appellants in the instant appeal) during 1976. The structure which Johnson and his co-workers identified for

prostacyclin is depicted in formula I, as follows:



I

As a part of the effort by appellants to determine the structure of prostacyclin itself, several new chemical compounds were prepared and biologically analyzed at Upjohn. Among these compounds were (5Z)-9-deoxy-6,9α-epoxy-5,6-didehydro-PGF_1, methyl ester, referred to at page 3, line 22 of appellants' specification. This methyl ester has as a chemical structure similar to that of prostacyclin, except that the carboxcyclic acid group is replaced by the methyl ester moiety. Refer to formula II below:



II

Unlike the biosynthetic preparation of Moncada, the methyl ester of prostacyclin could be prepared in an essentially chemically homogeneous form. Saponification of the methyl ester of prostacyclin with base lead appellants to additional novel chemical materials, i.e., various

salts of prostacyclin. Examples of the preparation of these salts are given in appellants' specification. Among these salts are, for example, the sodium salt of prostacyclin which is prepared by treating the methyl ester of prostacyclin with sodium hydroxide. The resulting material is an essentially chemical homogeneous free-flowing powder which appellant discovered to be vastly more suitable for human and veterinary pharmaceutical purposes than preparations of prostacyclin obtainable from biological sources, i.e., by the methods reported by Moncada and his co-workers in 1976.

The discovery of prostacyclin and its biological activity was made by Moncada and his co-workers independently of any work undertaken by appellants in the present appeal. Similarly, the preparation of the methyl ester of prostacyclin and the compounds of examples 1-3 in appellants' specification were undertaken in the chemical research laboratories of The Upjohn Company, independent from the discovery made by Moncada and his co-workers. Appellants did collaborate with Moncada and his co-workers in an effort to identify the structure of prostacyclin itself. In the course of this collaboration, appellants provided samples of chemical materials prepared by them, while Moncada and his co-workers provided samples of the biosynthetic materials prepared by them. In the course of this discovery, appellants and their co-workers were provided with proprietary information on the biosynthetic preparation, while Moncada and his co-workers were provided information on the chemical synthesis of the novel substances described in appellants' specification.

All this work eventually lead to the filing of patent applications by Moncada in the United Kingdom directed to the biosynthetic preparation of prostacyclin, material which Moncada characterized as "PGX" and applications of appellants' in the United States directed to the novel chemical compositions which they had prepared. Following the filing of a corresponding Moncada application in the United States and prosecution of both appellants parent application and the Moncada U.S. application to allowance, an interference was declared (Interference 100,116) which involved a phantom count directed to:

(a) prostacyclin itself,

(b) salts of prostacyclin, and

(c) lower alkyl esters of prostacyclin.

Moncada's claim corresponding to the count of this interference was directed to prostacyclin per se. Johnson's application neither described a preparation of prostacyclin per se nor claimed this substance and thus his claims corresponding to the count were limited to the salts of prostacyclin and lower alkyl esters of prostacyclin.

The Moncada application discloses both the salts and the lower alkyl esters of prostacyclin. However the esters of prostacyclin are not claimed by Moncada. These esters are the product of the chemical synthesis undertaken first by appellants, then reported to Moncada and his co-workers, and finally repeated by Moncada's co-worker, Dr. Norman Whitaker, prior to the filing of Moncada's application in the United States. Because the chemical preparation of prostacyclin esters was first done by appellants and later disclosed to Moncada's co-worker, Whitaker, Whitaker apparently did not regard himself the inventor of the esters of prostacyclin and no application of Whitaker purporting to claim these esters has apparently been filed in the United States on Whitaker's behalf. Similarly, the chemistry for preparing the esters of prostacyclin and their conversion to pharmacologically acceptable salts as disclosed by appellants to Whitaker is also not the subject of any Whitaker application in the United States. While this chemistry is disclosed in the Moncada application involved in Interference 100,116, it is presumably so disclosed only for best mode purposes. Claims which would relate to either the chemical process itself or to products of this process i.e., the crystalline form of the sodium salt of prostacyclin were all cancelled from the involved Moncada application in Interference 100,116 by Preliminary Amendment filed 1 September 1977.

In addition to the lack of a claim involved in Interference 100,116 encompassing the esters of prostacyclin, the involved Moncada claim does not encompass pharmacologically acceptable salts of prostacyclin either.

The Moncada application did contain such claims to the salts both generically and as species, although these claims were rejected finally by the Examiner in view of a publication by appellants which disclosed the free-flowing solid form of the sodium salts of prostacyclin. The Examiner held that the priority applications of Moncada did not describe the salts of prostacyclin in a manner commensurate with the requirements of 35 USC 112.

In any event the Examiner is in the process of dissolving Interference 100,116 on the ground that the subject matter of the count of that interference, at least insofar as it is directed to prostacyclin itself, encompasses a naturally occuring substance and is therefore not directed to patentable subject matter under 35 USC 101. Subsequent to the declaration of the interference with Moncada, appellants filed the above application with claims drawn to subject matter which they believed to be patentably distinct from the count of the interference in so far as the count of the interference can be taken to represent common invention of Moncada and appellants.

BRIEF SUMMARY OF THE REJECTION

The Examiner rejected the claims in this application on two bases:

(1) As being related to the same invention as the issue or count of Interference 100,116, and

(2) As being an attempt at double patenting with the sole claim of applicants' Serial Number 819,940, the application and claim involved in Interference 100,116.

SUMMARY OF THE ARGUMENT

The gist of appellants argument is that any rejection on the grounds of double patenting is premature since the rejection for double patenting is at best an obviousness-type double patenting and the involved claim in Interference 100,116 will not mature into a patent claim during the pendency of the interference content. Moreover, applicant has maintained that the present claims are patentable to him regardless of the outcome

of Interference 100,116 (award of priority, adverse award of priority, or dissolution without award of priority). Moreover, no estoppel can lie against appellants present claims inasmuch as they clearly could not have been made the subject of an issue in Interference 100,116 as they are clearly and undeniably subject matter which is unpatentable to Moncada. These arguments are all set forth in detail in appellants' Reply and Amendment of 31 March 1981.

DETAILED ARGUMENT

In addition to the remarks incorporated herein by reference from the 31 March 1981 Reply, appellants wish to re-emphasize the following:

I. No estoppel can arise based on the failure to propose the rejected claims as counts in Interference 100,116 in view of the inability to demonstrate "patentability" to Moncada as required under 37 CFR 1.231(a).

The rejected claims are directed to subject matter which could not have been an issue in Interference 100,116 under any circumstances. In these circumstances no issue of interference estoppel can arise even if priority in Interference 100,116 is awarded adversely to appellants. In order to fully appreciate the inability to either party in the interference to proposed counts such as those comprising the subject matter of the rejected claims, reference needs to be made to the file of Interference 100,116 and the involved Moncada application, S.N. 795,524, filed 10 May 1977. The Moncada application was filed more than four months subsequent to appellants' publication describing the prepartion of the sodium salt of prostacyclin as an essentially pure free-flowing powder. This publication describes specifically the subject matter of appellants claim 5, but also comes within the purview of appellants' claim 1. This publication described an essentially chemically pure material. Prior to appellants' publication Moncada or his co-workers had received from appellants samples of this material and had in fact tested it in their research laboratory. Moreover

one of appellants' co-workers, Dr. Norman Whitaker, had received a detailed briefing on the manner by which this material was prepared. Moncada in fact makes no representation that he is the inventor of these essentially chemically pure materials, in fact, the contrary is true. The claims in the original Moncada application as filed which related to essentially chemically pure materials or means for their chemical preparation (claims 15-19 of Moncada's S.N. 795,524) were cancelled from the Moncada preliminary to any substantive examination. Prior thereto, Moncada filed in the United Kingdom three applications (serial numbers 19384, filed 11 May 1976, 35151, filed 17 August 1976 and 36547, filed 3 September 1976). None of these applications contained any reference to any chemical means for preparing an essentially chemically pure salt of prostacyclin or prostacyclin esters. Rather, they are completely and expressly limited to the biosynthetic preparation of a material called "PGX". PGX is a potent platelet antiaggregatory substance and the active biological principle of PGX is prostacyclin. On this basis, one can conclude that Moncada was the inventor of prostacyclin itself, but the disclosure of the biosynthetic preparation of PGX did not necessarily enable one to prepare any essentially chemically pure material whatsoever, much less the free-flowing powder represented by the sodium salt of prostacyclin.

Interference 100,116 was declared because both parties had allowed compound per se claims. Moncada had an allowed claim to prostacyclin per se (even though the Examiner has now determined that inasmuch as prostacyclin is a naturally occuring hormonal substance, the claim is directed to an unpatentable natural product), while Johnson claimed prostacyclin salts and esters per se. Obviously, any preparation of prostacyclin, its salts, or its esters which exhibited some utility could be the subject of a proper patent application inasmuch as an "enabling" disclosure could be drafted.

However, mere knowledge of the fact that PGX existed and contained there within a novel pharmacologically-active biological principle would not enable those skilled in the art to derive appellants' pure material obtainable only by chemical means.

Thus knowledge available to appellants during the motion period of Interference 100,116 indicated that Moncada did not even regard himself as the inventor of these chemical materials and even if he had would not have been entitled to rely on his British application, wholly devoid of the chemical preparation of anything, in support of a priority claim under 35 USC 119. Lacking the ability to benefit from the earlier filed applications in the United Kingdom, Moncada's claims to the salts of prostacyclin as described in the rejected claim would clearly have been barred in view of the intervening Johnson publication. In summary, the interference was declared because each party was entitled, at least in the Examiner's view, to make compound per se claims directed to the same invention (even though there was no allowed overlapping subject matter). For such claims the manner of preparation, biosynthetic, or otherwise was immaterial. However, appellants' rejected claims are more limited, being directed to materials, not the compounds per se, which could only have been derived from chemical synthetic methods not regarded by Moncada as his own invention. Just as Moncada ought to be entitled to claim the PGX residue (a preparation which clearly does not occur in nature and clearly cannot be derived from the chemical invention of appellant), appellants ought to be entitled to claim the chemical residue consisting of essentially pure salts of prostacyclin. The divergent sources of invention here permit the maintenance of an interference only because in addition to each party's unique "residue", the parties were further believed by the Examiner to be entitled to claim the corresponding chemical materials per se.

II. The absence of "double patenting" during the pendency of Interference 100,116.

Given that the present claims could not have been made the subject of Interference 100,116, this subject matter ought to be patentable to appellant, unless under some theory of 35 USC 102(g)/103 prior art, Moncada's work would either anticipate or render obvious appellants' rejected claims. However, even if all Moncada's work were prior art

and that prior art entitled Moncada to a patent on all claims now pending in the Moncada application involved in Interference 100,116, appellants respectfully assert that their present claims would be patentable. In this case whatever subject matter could conceivably be prior art under 35 USC 102(g)/103 would be limited to materials prepared biosynthetically. Due to the instability of prostacyclin, the minute amount of material which can be prepared biosynthetically and the impossibility of chemical purification of PGX once prepared, the Moncada "prior art" would not be enabling insofar as it relates to essentially chemically pure materials. Simply put, appellants are claiming something which knowledge of all Moncada's work as prior art would not enable one of ordinary skill in the art to achieve.

Since loss of the interference cannot render the rejected claims unpatentable, the remaining question is whether they represent a double patenting situation which should be sustainable in this appeal. However, as long as Interference 100,116 is being maintained, a double patenting rejection in the present application is premature. Since there are no organic compound per se claims in the present application, this application is not directed to the same subject matter as appellants' parent application involved in Interference 100,116. At most, it is obvious in view of the claim in the parent application and therefore a terminal disclaimer may at some point become appropriate. However a terminal disclaimer is clearly not appropriate since actual issuance of the patent on the parent application will be deferred until, at the earliest, the terminal of Interference 100,116. Since appellant is clearly electing to proceed with prosecution of the present application and reversal of the Examiner's rejection on all other grounds would result in the issuance of a patent on the rejected claims prior to the claim involved in Interference 100,116, the double patenting rejection is premature and ought to be made, if at all, in the involved application following termination of the interference.

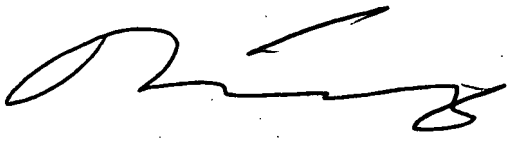
CONCLUSION

While appellants might have waited until the termination of Interference 100,116 to begin prosecution of the subject matter of

the present claims appellants own interests, as well as those of the public at large, ought to encourage prompt issuance of United States patents on non-interferring subject matter and where such non-interferring subject matter is patentable regardless of the outcome of the interference. Any delay in the issuance of the patent leads to hardship to all parties. This is precisely a situation where a prompt determination ought to be made that whatever the merits of the issue in Interference 100,116 they do not impact on the present claims in a manner which would deny appellants' right to the prompt issuance of the United States patent.

Reversal of the Examiner's rejections is accordingly respectfully solicited.

Respectfully submitted,



Robert A. Armitage, Attorney
Registration No. 27,417
(616) 385-7345

RAA:DAT

18 January 1982

Kalamazoo, MI 49001